November 21, 1949.

Dr. Frank H. Dickey,
Kerckhoff Laboratories of Biology,
California Institute of Technology,
Pasadena, California.

Dear Dr. Dickey:

I was very much interested in your recent paper on the mutagenic action of peroxides. One of the less crucial, but pertinent, remarks made therein was that the largest numbers of mutants were obtained with treatments that killed 60-80% of the spores. Giles and Mrs. Lederberg had found the same general result in their radiation studies, and like yourself were, perhaps, mildly surprised that the optimum output was obtained with so mild treatments. After a little reflection, however, this result turned out to be quite rational, and on the chance that you had not noticed it, I thought you might be interested in the following derivation [the conclusion of which was cited in my review article in Heredity, II, p. 165.]

The assumption is made that the probability of a lethal "hit" is proportional to the probability of a mutational "hit", for any dose. In the following, m_o is the initial number of mutants, k_m is the rate of mutation induction, k_1 is the rate of killing, and t is the effective dose [measured either from the kill or the mutations]. If $k_m t$ is small, as it will be, it is a sufficiently accurate measure of the accumulated mutants [viable or not], and we have:

$$m_t = (m_o + k_m t)\, e^{-k_1 t} = (m_o + k_m t)\, S \quad \text{[survival ratio]}$$

To maximize, we have

$$dm/dt = 0 = k_m S - k_1 (m_o + k_m t) S$$

$$k_1 t = 1 - k_1 m_o / k_m$$

or $$S = e^{-1} \left[e^{k_1 m_o / k_m} \right]$$

For $m_o \doteq 0$, which we can take in the present instance, the bracketed term can be neglected, and we have $S_{opt} = 1/e = .37$. For $m_o \neq 0$ we would have, of course S_{opt} as high as 1.0, with the condition that $k_1 m_o < k_m$ if any increase can be obtained at all.

Although this conclusion has been reaced empirically, it is worthwhile pointing out the principle for any investigation in which the production of an absolute augmentation of mutants (which can, e.g., be absolutely selected for) is the desideratum.

I still have hoped of finding time to repeat some of your specific absorption experiments. I am still undecided how I would be able to apply it to the system in which I would be most interested- galactosidase- particularly the problem of removing excess lactose from the gel. Have you attempted, in your dye experiments, to use simple water elution?

Thank you for the experimental details which you sent in your letter. I wonder if you could enlighten me a bit further on the technique of methanol extraction. Is this done in the standard way, at the boiling point of methanol? or is it necessary to use some artifice to keep the temperature down?

Finally, could you tell me anything of your experimental attempts with heterogeneous catalysis, mentioned in your PNAS paper?

Sincerely yours,

Joshua Lederberg